1.2. The action objects to the top and left margins of Figs. 1B, 6B, 9B and 17, the line quality in Figs. 12B and 12C, and to the labeling of a view on Fig. 3 (OA §3).

We submit replacement copies of Figs. 1B, 6B, 9B, 17, 12B and 12C which, we believe, satisfy the margin and line quality requirements. We submit a proposed drawing correction of Fig. 3. We will make conforming amendment to the specification once the proposed correction is approved.

1.3. An Abstract is enclosed (OA §4).

1.4. We have amended claims 8, 9 and 23 to meet the stated objections (OA §§5-7).

2. Prior Art Issues (OA §16-20)

Claims 1-24 stand rejected as anticipated by or obvious over Adams et al. (WO96/04404). Claims 1-6, 8-10 and 12-24 stand rejected as anticipated by Adams, USP 6,060,288.[1] Claim 26 stands rejected as obvious over Adams '288 in view of Schumm. These rejections are respectfully traversed.

Claim 1 has been amended to incorporate the limitations of both claims 3 and 5.

Both Applicant and Adams contemplate amplifying a "target nucleic acid molecule" (we also call it a "template"; Adams calls it a "first nucleic acid") by annealing first and second primers to it (Adams' second and third nucleic acids), forming elongation and amplification products, and so forth.

However, we differ fundamentally in how we handle the situation in which a sample comprises a plurality of different target nucleic acid molecules.

In Adams' method, the primers (the second and third nucleic acids) hybridize to endogenous portions (sequence "a" of strand **25**; sequence "b" of strand **27**) of the target nucleic acid

[1] The two Adams references relied on here are related. Adams, USP 6,060,288 issued on 08/800,840, which was a continuation-in-part of 08/776,859 the national stage of PCT/US95/09905, published as Adams WO96/04404.

molecule (the first nucleic acid). Hence, for each different target nucleic acid molecule, amplification requires a corresponding pair of primers. Generally speaking these will be different for each target molecule.

Thus, at page 9, lines 3-9, Adams WO96/04404 states

> One embodiment of the present method features a support with many sets of second and third nucleic acids, with each set directed to a different first nucleic acid. Preferably, each set of second and third nucleic acids are positioned in discrete areas of the support. Each support may comprise a plurality of sets to a plurality of first nucleic acids and targets.

If the number of different target nucleic acid molecules is large, it is impractical to provide enough pairs of primers so that every DNA template in the sample will be amplified. The templates for which there is no matching pair of primers will be unamplified, and therefore, lost and forgotten.

In Applicant's method, at the time of amplification, each target molecule comprises first and second parts to which first and second primers can anneal. However, in the embodiments originally claimed in claim 3, and now integral to amended claim 1, these first and second sequences are not native to the target molecule but rather were added to the "given nucleic acid sequence to be amplified" (the "third part" referred to on page 11). This limitation has been imported into amended claim 1, although the word "ligated" is used in place of "added" in view of the non-art rejection of claim 3.

The exogenous character of the first and second sequences is expressly recited in amended claim 1, but the "addition" step by which they are incorporated into the target molecule is not expressly recited. However, it is so recited in new claim 66.

This exogenous primer binding site feature is not disclosed or suggested by either Adams reference.

Claims 23-25, 67 and 70-71 contemplate amplification of a plurality of different "given" sequences.

Because our first and second sequences are exogenous to the third sequence (the sequence to be amplified), we are at liberty to choose the first and second nucleic acid sequences to be the same for each of the different nucleic acid molecules, as required by claims 25 and 71. This means, in turn, that with one pair of primers (first and second primers hybridizing to the common first and second nucleic acid sequences), we can amplify the entire library of target nucleic acid molecules (and hence all of the different original nucleic acid sequences to be amplified). See new claims 70 and 71.

One may, of course, deliberately divide the sample into subsets by some criterion, and use one pair of first and second sequences (and hence one pair of primers) for each subset. This was the thinking underlying claims 9 and 10; note that claim 10 contemplates two subsets.

By virtue of the use of exogenous first and second sequences, and complementary pairs of primers, amplification products, and hence sequence information for those products, are obtainable for every DNA template in the sample.

3. Non-Art Issues (OA §9-15)

Claims 3, 4, 13, 18, 20 and 23-26 stand rejected for indefiniteness (§112 ¶2).

3.1. Claim 3 has been cancelled. Claim 4 no longer recites "to which have been added".

Claim 3, as originally filed, recited that "said target nucleic acid is produced by providing a given nucleic acid sequence to be amplified... and adding thereto a first nucleic acid sequence and a second nucleic acid sequence". The clear implication was that the first and second nucleic acid sequences were exogenous to the given sequence.

In the discussion of target nucleic acid molecules at p. 11, the first and second nucleic acid sequences were identified as the "first and second parts of the target nucleic acid molecules", and the given nucleic acid sequence to be amplified

was identified as the "third part". This is the result of the aforementioned addition.

At page 12, lines 5-8, Applicants teach that target nucleic acid molecules can be provided by ligating two or more parts together. This confirms that the parts were originally separate molecules. Since the term "ligating" has a specific meaning in the art, and is used in the specification, we have replaced "added" with --ligated-- in transferring claim language from claim 3 to claim 1.

3.2. We have deleted "(e.g. in a grid pattern)" from claim 13, but this has been made the subject of new dependent claim 68. Likewise, "e.g. fluorescent labels or radiolabels" has been transferred from claim 18 to new dependent claim 69.

3.3. We have amended claim 19 to recite that the treatment occurs after step (E) of claim 1. This then resolves the issue concerning claim 20.

3.4. As suggested by the examiner, claims 23 and 24 are directed to amplifying a plurality of different given nucleic acid sequences using a target nucleic acid molecule as a template. The different nucleic acid sequences are each part of one target nucleic acid molecule. We prefer to speak of amplifying the "given sequences", rather than of amplifying the target molecule, because the amplification of the target molecules is the claimed means by which the goal of amplifying the "given" sequence is achieved.

Claims 23-25 have been amended to clarify that the "different nucleic acid sequences" are the "given" sequences of claim 1, i.e., part of the target molecule.

With regard to claim 25, the Examiner is failing to distinguish between the sequence to be amplified (which can differ from one target molecule to the next) and the first and second sequences (which, per claim 25, are the same for each target molecule).

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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Enclosures
-Proposed correction to Fig. 3 (corrections in red ink)
-Substitute Figs. 1B, 6B, 9B, 12B, 12C and 17
-Abstract of the Disclosure

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Drawings

Corrected Fig. 3 is enclosed.

In the Specification

An abstract of the disclosure is enclosed.

In the claims:

Claims 3 and 5 have been cancelled.

Claims 67-73 have been added.

Claims 1, 4, 8, 9, 13, 18, 19, 23, 24 and 25 have been amended as follows:

1 (Twice Amended). A method of nucleic acid amplification, comprising the steps of:

A) providing (i) a plurality of primers that are immobilized but that have one end exposed to allow primer extension and (ii) a single stranded target nucleic acid molecule which comprises a given nucleic acid sequence to be amplified, and first and second nucleic acid sequences which have been ligated to the given sequence;

B) allowing a single stranded target nucleic acid molecule to anneal to one of said plurality of primers over part of the length of said single stranded nucleic acid molecule and then extending that primer using the annealed single stranded nucleic acid molecule as a template, so as to provide an extended immobilized nucleic acid strand;

C) separating the target nucleic molecule from the extended immobilized nucleic acid strand;

D) allowing the extended immobilized nucleic acid strand to anneal to one of said plurality of primers referred to in step A) and then extending that primer using the extended immobilized nucleic acid strand as a template, so as to provide another extended immobilized nucleic acid strand; and optionally,

E) separating the annealed extended immobilized nucleic acid

strands from one another,

wherein said first nucleic acid sequence hybridizes to one of said plurality of primers and said second nucleic acid sequence is complementary to a sequence which hybridizes to one of said plurality of primers,

wherein said first and second nucleic acid sequences are provided at the 3' and 5' ends of said single-stranded target nucleic acid molecule.

4 (Twice Amended). A method according to claim 1[; wherein said single-stranded target nucleic acid comprises a given nucleic acid sequence to be amplified (which sequence may be known or unknown) to which have been added a first nucleic acid sequence and a second nucleic acid sequence;] wherein said first nucleic acid sequence hybridizes to one of said plurality of primers and said second nucleic acid sequence is the same as the sequence of one of said plurality of primers.

6 (Amended). A method according to claim [3] 1, wherein a tag is also [added] ligated to the given nucleic acid sequence, said tag enabling amplification products of the given nucleic acid sequence to be identified.

8 (Amended). A method according to claim 1, wherein the plurality of primers comprises at least two different types of [primer] primers, one type having a different sequence from another type.

9 (Amended). A method according to claim 8, wherein the plurality of primers consists of 2^n different types of [primer] primers; wherein n is an integer.

13 (Twice Amended). A method according to claim 1, wherein the primers are located in a predetermined arrangement [(e.g. in a grid pattern)].

18 (Twice Amended). A method according to claim 1, wherein said primer extension results in the incorporation of one or more detectable labels [(e.g. fluorescent labels or radiolabels)] into extended immobilized nucleic acid strands.

19 (Twice Amended). A method according to claim 1, further

including the step, after step (E), of treating one or more extended immobilized nucleic acid strands so as to release a nucleic acid molecule or a part thereof.

23 (Amended). A method according to claim 1, when used to amplify a plurality of different given nucleic acid sequences, each such given sequence being a part of a target nucleic acid molecule.

24 (Amended). A method according to claim 23, when used to amplify a plurality of different given nucleic acid sequences simultaneously, each such given sequence being a part of a target nucleic acid molecule.

25. A method according to claim 23, wherein said different given nucleic acid sequences are each provided with a first and second nucleic acid sequence [as described in any of claims 3 to 5], said first and second nucleic acid sequences being the same for the each of the different single stranded nucleic acid [sequences] target molecules comprising said given nucleic acid sequences.